REMARKS

Amendment of Claims

Claims 2, 3, 11, 17 and 28-56 have been cancelled. The subject matter of claims 2 and 3 has been introduced into claim 1. The subject matter of claim 17 has been introduced into claim 16.

Rejection of Claims and Traversal Thereof

In the October 3, 2007 Office Action:

1. claims 1, 2, 5-10, 12-13, 16, 20-26, 38-39, 41-44, and 46-49 were rejected under 35 U.S.C. 102 (b) as being anticipated by Vo-Dinh (U.S. Patent No 5,814,516, hereinafter Vo-Dinh);

2. claims 1, 4-8, 10-14, 38 and 41-48 were rejected under 35 U.S.C. 102 (e) as being anticipated by Lakowicz (U.S. Patent Application No. 2002/0160400, hereinafter Lakowicz 1);

3. claims 1, 5-7, 11-14, 38, and 41-48 were rejected under 35 U.S.C. 103(a) as being unpatentable over Carron, et al. (U.S. Patent No. 6,770,488, hereinafter Carron);

4. claims 4, and 19 were rejected under were rejected under 35 U.S.C. 103(a) as being unpatentable over Carron, in view of Lakowicz, "Radiative Decay Engineering: Biophysical and Biomedical Applications," Analytical Biochemistry, 2001, Vol. 298, pp 1-24 (hereinafter Lakowicz 2);

5. claims 3, 15, 17-18, 40 and 49 were rejected under 35 U.S.C. 103(a) as being unpatentable over Carron, et al. in view of Cao, et al. "Nanoparticles within Raman Spectroscopic Fingerprints for DNA and RNA Detection," Science, Aug 2002, Vol. 297, pp 1536-1540 (hereinafter Cao);

6. claims 4, 11, 19 and 45 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh in view of Lakowicz 2;

7. claims 3, 15, 17-18, 40 and 49 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh in view of Cao; and

8. claims 14, 27, and 48 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh in view of Carron.

These rejections are hereby traversed and reconsideration of patentability of the pending claims is therefore requested in light of the following remarks.

Rejections under 35 U.S.C. 102 (b) or 102(e)

1. Claims 1, 2, 5-10, 12-13, 16, 20-26, 38-39, 41-44, and 46-49 were rejected under 35 U.S.C. 102 (b) as being anticipated by Vo-Dinh. Applicants insist that this reference is not anticipatory.

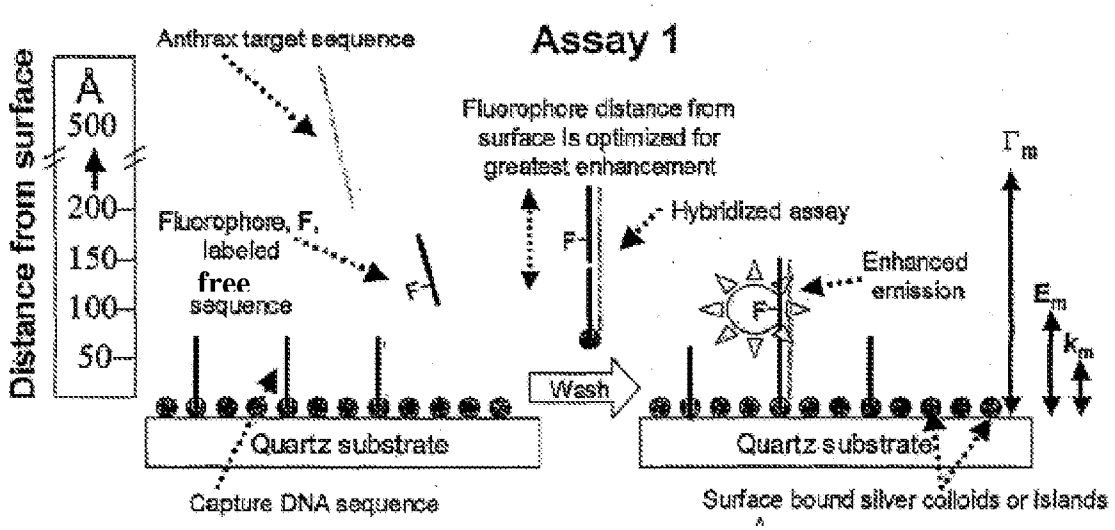
Applicants' claim 1 recites the following:

> 1. A method for detecting *B. anthracis* in a sample, the method comprising:
>
> a) providing a system comprising:
> a layer of immobilized metal particles positioned on a surface substrate, wherein the immobilized metal particles have attached thereto a captured nucleotide sequence probe complementary to a first portion of a nucleotide sequence of the *B. anthracis*; and
> b) contacting the sample with the captured nucleotide sequence probe, wherein any *B. anthracis* in the sample having a nucleotide sequence complementary to the captured nucleotide sequence probe binds to the captured nucleotide sequence probe; and
> c) contacting any bound *B. anthracis* sequence with a free nucleotide sequence probe, wherein the free nucleotide sequence probe has an affinity for a second portion of the nucleotide sequence of *B. anthracis* and has attached thereto a fluorophore, and wherein binding of the free nucleotide sequence probe to the second portion of *B. anthracis* nucleotide sequence causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission when excited by an irradiating source.

Notably, the important aspect of the present invention relates to the use of two separate and distinct probe sequences (a captured and free nucleotide sequence probes) that are not complementary to each other but instead are complementary to separate and distinct portions of the target nucleotide sequence. Importantly, with the specific use of two probes sequences that are complementary to different sections of the target nucleotide sequence, the free probe sequence includes a fluorophore that is positioned a distance from the metallic surface to provide for a more sensitive test with increased reliability even when the level of anthrax in the sample is not identifiable by other less sensitive tests.

The Office proposes that U.S. Patent No. 5,814,516 defeats the novelty of the presently claimed invention. Applicants vigorously disagree because this reference does not disclose, teach or suggest each and every element of the presently claimed invention.

Initially it should be noted that there is no disclosure relating to anthrax by Vo-Dinh. Further the systems described in Figures 2 and 6 of Vo-Dinh do not disclose, teach or suggest the presently claimed invention. As stated above, applicants' system includes the use of two separate and distinct probe sequences (a captured and free nucleotide sequence) that are complementary to different sections of the target nucleotide sequence. The free nucleotide probe sequence includes a fluorophore positioned a distance from the metal surface. This is shown below by applicant's Figure 1.



In contrast, Vo-Dinh shows entirely different systems wherein placement of the metal surface from the fluorophore is not even important. Figure 2 shows a probe 6 with a label while Figure 6 shows that the labeled sequence is immobilized. Further, there are only two sequences. Clearly by viewing these systems, it is evident that neither describes the assay of the present invention as shown above.

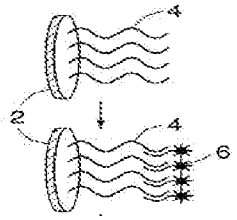


Figure 2

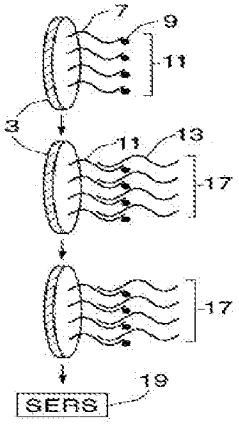


Figure 6A

Applicants' claim 16 recites the following:

16. (Currently amended) An assay method for detecting a target pathogen in a sample, the method comprising:

a) providing a system comprising:
an immobilized metallized layer positioned on a surface substrate, wherein the immobilized metallized layer has attached thereto an immobilized capture nucleotide sequence probe complementary to a known nucleotide sequence of the target pathogen;
b) contacting the sample with the immobilized capture nucleotide sequence probe, wherein the nucleotide sequence of the target pathogen binds to the immobilized capture nucleotide sequence probe;
c) contacting the bound nucleotide sequence of the target pathogen with a free nucleotide sequence probe, wherein the free nucleotide sequence probe is complementary to a known nucleotide sequence of the target pathogen, wherein the free nucleotide sequence probe has attached thereto a fluorophore, wherein the free nucleotide sequence probe further comprises a metal colloid attached thereto and positioned for sandwiching the fluorophore between the metal colloid and immobilized metal particles on the surface substrate when the nucleotide sequence of the target pathogen is bound to the immobilized metal particles, wherein binding of the free nucleotide sequence probe to the nucleotide sequence of the target pathogen causes the fluorophore to be positioned a sufficient distance from the immobilized metallized surface and metal colloid to enhance fluorescence emission when excited by an irradiating source; and
d) identifying the target pathogen by fluorescence emission by irradiating the system with an irradiating source to excite the fluorophore.

Thus this system has the advantage of introducing a second metallic colloid or particle attached to the free nucleotide sequence probe so that the fluorophore can be sandwiched between the metallic surface of the substrate and the metallic colloid. In conclusion the Vo-Dinh reference in not an anticipatory reference and applicants request that the Office reconsider and withdraw this rejection under section 102.

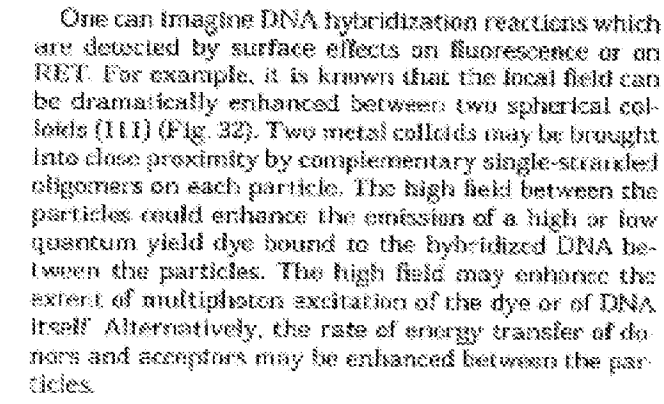
2. Claims 1, 4-8, 10-14, 38 and 41-48 were rejected under 35 U.S.C. 102 (e) as being anticipated by Lakowicz 1. Applicants submit that this reference suffers from the same shortcomings as that of Vo-Dinh, and as such, request that the Office reconsider and withdraw this rejection under section 102.

Rejections under 35 U.S.C. 103 (a)

3. Claims 1, 5-7, 11-14, 38, and 41-48 were rejected under 35 U.S.C. 103(a) as being unpatentable over Carron. Applicants insist that the cited reference does not defeat the patentability of the presently claimed invention. Claims 38, and 41-48 have been cancelled herein and the subject matter of claim 3 has been introduced into claim 1. The Office has already admitted that Carron does not in any way teach a method for detecting *B. anthracis* in a sample, and as such, Carron does not in any way teach the claimed subject matter of claim 1 and all claims depending therefrom. Accordingly, applicants request the withdrawal of this rejection.

4. Claims 4, and 19 were rejected under were rejected under 35 U.S.C. 103(a) as being unpatentable over Carron, in view of Lakowicz 2. Applicants insist that the proposed combination does not in any way discloses, teaches or suggests the subject matter in amended claims 4 and 19. Claim 4 depends from claim 1 and neither Cannon nor Lakowicz 2 teaches a method for detecting *B. anthracis* in a sample. Claim 19 depends from amended claim 16, which now recites an assay system that introduces a second metallic colloid or particle attached to the free nucleotide sequence probe so that the fluorophore can be sandwiched between two metallic particles.

Lakowicz 2 describes hybridization methods but limits such discussion to two sequences that complementary to each other wherein each is attached to a metal particle, as shown below.



One can imagine DNA hybridization reactions which are detected by surface effects on fluorescence or on RET. For example, it is known that the local field can be dramatically enhanced between two spherical colloids (111) (Fig. 32). Two metal colloids may be brought into close proximity by complementary single-stranded oligomers on each particle. The high field between the particles could enhance the emission of a high or low quantum yield dye bound to the hybridized DNA between the particles. The high field may enhance the extent of multiphoton excitation of the dye or of DNA itself. Alternatively, the rate of energy transfer of donors and acceptors may be enhanced between the particles.

This method would not provide any analysis because both complementary oligomers have to be available for labeling before the reaction. Intuitively, in a testing mode, one does not label a suspected sequence because one does not know if it is in the sample. The above paragraph does discuss the combining of two complementary sequences that include a metallic component but there is no discussion about two separate sequences both of which are complementary to a **third target sequence.** Applicant realizes that there is a subtle difference between the two systems but this subtle difference is what improvement inventions usually include because an inventor recognizes a problem and finds a solution. In the present invention, a more sensitive testing assay was required to determine low levels of anthrax which is not possible with any of the previous systems. By optimal placement of the fluorophore on the free nucleotide sequence, the binding with the anthrax sequence provides an optimal spacing from the metal surface and optimal signal, as discussed at page 28 of the present specification.

There is no indication in the Lakowicz 2 reference of any disclosure relating to the two different nucleotide sequences probes, one immobilized on a metallic particle and the other with a fluorophore, wherein both nucleotide sequences bind to the target nucleotide sequence as in the present invention. As such, applicants submit that the proposed combination does not in any way defeat the patentability of the presently claimed invention.

5. Claims 3, 15, 17-18, 40 and 49 were rejected under 35 U.S.C. 103(a) as being unpatentable over Carron in view of Cao. Applicants submit that this proposed combination does not establish a *prima facie* case of obviousness.

Initially it needs to be noted that Carron has developed a new system where analyte coated metal colloids are coated with analyte binding agents and then the colloids and binding agents are subjected to a **desiccation process**. This desiccation process is the heart of the Carron invention because it provides for

a quantitative method of determining binding ligands. Clearly the Carron reference discusses the problems related to desiccation and the absolute inability to reconstitute some binding agents on metal colloids Notably one skilled in the art would easily recognized that a nucleotide sequence attached to the metal colloid would likely not survive the desiccation process.

However, even in light of the warning by Carron relating to desiccation, the Office has attempted to combine the Carron reference with Cao. Notably Cao uses a surface substrate (**such as glass with no metal coating**) that is coated with nucleotide sequences. This surface substrate with the nucleotides attached thereto is kept in **a humidity chamber** at room temperature and then is contacted with oligonucleotide functionalized nanoparticles that include the following (1) Au nanoparticles, (2) a DNA sequence complimentary to the surface attached nucleotide sequences and also has attached a Cys3 label. Ag containing solution is then added to the assay to increase the size of the metal presence of the Au metal colloid. Notably, this additional metal particle is not attached to an additional probe but in fact, the solution containing the Ag^{-} attaches to the same nucleotide sequence that is attached to the Au particle. Thus, one questions how a fluorophore signal can be increased especially in light of the fact that it is well known that if the fluorphore is to close to the metallic surface the signal is quenched.

Even in light of the *KSR* decision the Office is still required to present a *prima facie* case of obviousness, which clearly has not been established by the proposed combination. Further, It should be noted that it is incumbent on the Office to view applicants' claimed invention as a whole. *In re Wesslau*, 174 U.S.P.Q. 393 (CCPA 1965). Concurrently, the Office **must** consider the inventions of any cited references in their respective entireties. Certain individual features from the references may not be arbitrarily chosen (while equally arbitrarily discarding other disclosed features) to merely lump together disparate features of different references as a mosaic in an attempt to meet the features of the rejected claims. Thus, the Office is not allowed to pick and choose just certain parts of different references and combine them, but instead, the references in their entirety must be considered.

Accordingly, the Office must recognize that Carron describes a critical step that includes the use of desiccation to provide capture metal colloids having long term shelf live and that may be used in the quantitative methods of Carron. In contrast, Cao teaches the use of non-metallic surface substrates that include nucleotide sequences attached thereto.

Applicants submit that if the teachings of Carron and Cao, are combined, even though there is no suggestion for such a combination, each system will be rendered unsatisfactory for its intended use

and/or change the principle of operation. According to the court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification and the Office has not established a *prima facie* case of obviousness.

For instance, if the teachings of Carron that describes a critical step including the desiccation of the metal colloids is combined with the Cao requirement of a nucleotide sequence to be used not only on the surface substrate, then the desiccation of the Cao surface substrate will render the Cao invention either inoperatable or no longer functionable as intended. In fact, applicants doubt it will function at all in light of the fact that the desiccation process will likely alter the nucleotide sequences to the point of no longer being useful or functioning.

Likewise, Cao expects the surface substrate to be stored in a humidity chamber at room temperature. Clearly, if this humidity chamber is added to the Carron system then the Carron system which requires the metallic colloids be dried to remove all moisture will no longer function as intended. As such, combining the teachings set forth in both references will render each individual invention unsatisfactory for its intended use or change its principal of operation.

Further, the Office has not identified any objective or specific motivation or suggestion in the cited references that would motivate one skilled in the art to combine the references. Thus, the Office seems to be merely reinterpreting the prior art in light of applicants' disclosure, in order to reconstruct applicants' claimed invention, but without any instructional or motivating basis in the references themselves. Such approach is improper and legally insufficient to establish any *prima facie* case of obviousness.

In conclusion and in light of the above discussion, applicants contend that the Office has not met its burden of establishing a *prima facie* case of obviousness. Accordingly, applicants respectfully request that this rejection, on the basis of obviousness, be withdrawn.

6. Claims 4, 11, 19 and 45 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh in view of Lakowicz 2. Applicant insists that this rejection suffers from the same shortcomings as other rejections. Namely, neither Vo-Dinh nor Lakowicz 2 teaches or suggests the limitations of claim 1 from which claims 4 and 11 depend therefrom. Claim 19 depends from amended claim 16, which now recites an assay system that introduces a second metallic colloid or particle attached to the free nucleotide

sequence probe so that the fluorophore can be sandwiched between two metallic particles. As discussed above in paragraph 4, Lakowicz 2 only describes the combining of two complementary sequences that include a metallic component but there is no discussion about two separate sequences both of which are complementary to a **third target sequence.** As such, applicants insist that the proposed combination does not in any way teach or suggest the presently claimed invention and requests the withdrawal of this rejection under 103.

7. Claims 3, 15, 17-18, 40 and 49 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh in view of Cao. Applicants submit that this combination does not render the presently claimed invention as obvious. Notably, claims 40 and 49 have been cancelled herein.

Notably, this combination suffers from the same shortcomings as described in paragraph 5 set forth above, that being, the combination will render each invention unsatisfactory for its intended use or change its principal of operation. Again the Office must remember that it is not allowed to pick and choose only certain parts of a cited reference while overlooking other parts of the references. Instead, the Office must look at each reference in its entirety for all that it teaches. For example, the Vo-Dinh reference clearly teaches the need of a metallized surface substrate, but Cao does not teach such a metallized surface. The free nanoparticles in Cao include a metal colloid with a fluorophore and additional Ag attachments, but the free probe in Vo-Dinh includes only a fluorophore.

So now looking at these two references, which parts does the Office want one skilled in the art to combine. Keeping in mind that this skilled person does not have applicants' specification to help in the process of picking and choosing. Clearly, if the non-metallized surface of Cao is combined with the non-metallized probe of Vo-Dinh then the Vo-Dinh system will include **no** metallic surfaces at all and clearly will not function as intended. One questions what will happen to the Vo-Dinh system if the probe of Cao is used along with the Ag solution. Again, the Office is not allowed to overlook the Ag solution that binds to the nucleotide sequence along with the Au already bound thereto. Will this Ag solution also add additional silver to the substrate of Vo-Dinh. If so will there be so much metal build up that if fact the signal from the fluorophore will be quenched. Clearly, these issues need to be addressed by the Office. Applicants suggest that since there is no suggestion in either reference as to which parts should be combined, the Office is using applicants' specification as a blueprint in an attempt to recreate applicants' claimed invention. This is unacceptable.

The Office's attention is directed to the Federal Circuit's decision in *Environmental Designs v. Union Oil Co. of Cal.*, 218 USPQ 865 (Fed. Cir. 1983), where the court stated:

> " That all elements of an invention may have been old (the normal situation), or some old or some new, or all new, is however, simply irrelevant. Virtually all inventions are combinations of old elements. A court must consider what the prior art as a whole would have suggested to one skilled in the art."

Thus, the fact that isolated elements of an invention are "disclosed" in the prior art is alone insufficient. The test is not whether isolated "elements" are known, but rather whether the subject matter of the invention "as a whole," in light of all the teachings of all the cited references in all of their entireties, would have been obvious to one of ordinary skill in the art at the time the invention was made.

In light of the foregoing discussion and the fact that all of claimed limitations are not disclose or suggested by the cited combination and/or the proposed combination will render the inventions of both references either inoperable or no longer functioning as intended, it is clear that the Office has not met its burden of establishing a *prima facie* case of obviousness.

8. Claims 14, 27, and 48 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh in view of Carron. Namely, neither Vo-Dinh nor Carron or the combination thereof teaches or suggests the limitations of claim 1 or claim 16 from which claims 14 and 27 depend, respectively. As such, if the combination does not in any ways teach the limitation of the independent claims then the Office's is likely using applicants' specification as a blueprint to pick and choose parts of different references with the hope of somehow meeting the necessary requirements to show obviousness. Clearly, in this case that attempts was not successful. Applicants request the withdrawal of this rejection under section 103.

Fees Payable

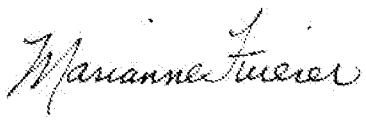
No fees are due, however, if any additional fee is found due for entry of this amendment, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner

Braughman reconsider the patentability of the pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. If any issues remain outstanding incident to the allowance of the application, Examiner Braughman is requested to contact the undersigned attorney at (919) 286-8089.

Respectfully submitted,



Marianne Fuierer
Reg. No. 39,983
Attorney for Applicants

Moore & Van Allen, PLLC
Telephone: (919) 286-8000
Facsimile: (919) 286-8199